Case Report

Pulmonary Langerhans' Cell Histiocytosis Masquerades as Miliary Tuberculosis in an Adolescent Boy

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Abstract

INTRODUCTION*: Langerhans cell histiocytosis is a rare histiocytic disorder of unknown etiology that commonly affects young adults at 20-40 years of age. Pulmonary involvement occurs as a single-system disease and is characterized by focal Langerhans cell granulomas infiltrating and destroying distal bronchioles.*

CASE REPORT*: We are reporting a case of a 16-year-old young boy who was a non-smoker referred to our hospital with persistent hypoxemia. He was misdiagnosed earlier to have tuberculosis based on a chest X-ray. Later on, a High-resolution computerized tomography of thorax revealed multiple cystic lesions with reticulonodular opacities predominantly in the upper lobes, with regional sparing of the costophrenic recess. LCH was suspected based on radiology and was given pulse doses of methylprednisolone. Minimal improvement was observed in hypoxemia. The patient was lost to follow up.*

CONCLUSION: *Langerhans cell histiocytosis is a rare, multi-systemic disease, in adults, almost exclusively in smokers and its diagnosis is often missed or delayed. It has a high rate of misdiagnosis. It can be confirmed only by pathological biopsy and radiology. There hasn't been any specific treatment, combined chemotherapy for multisystem lesions, radiotherapy or surgical operation for unifocal lesion may improve the therapy.*

KEYWORDS: *Langerhans' cell histiocytosis, non-smoker, cystic lesions, reticulonodular opacities.*

ABBREVIATIONS: *LCH- Langerhans' cell histiocytosis, LC- Langerhans' cell, CT- computerized tomography.*

Introduction

Langerhans' cell (LC) histiocytosis (LCH) encompasses a group of disorders of unknown origin with widely diverse presentations and outcomes, characterized by infiltration of involved tissues by a large no of LC's, often organized into granulomas. **(**1**)**. Several organ systems may be involved including the lungs, bones, skin, pituitary gland, liver, lymph nodes and thyroid. **(**2**)** The term "Pulmonary Langerhans' cell histiocytosis" is used to refer to disease in the adults, that affects the lung, either alone or in association with other organs **(**3**)**.

Case Report

A 16-year-old boy was referred to our hospital in view of persistent hypoxemia. He had a cough with expectoration, chest pain and breathlessness for the past 2 months with no history of weight loss or loss of appetite. The boy had no history of smoking. Based on his chest X-ray, he was assumed to have miliary tuberculosis and was started on Anti TB medicines. But the boy did not find any relief in symptoms. The patient was still tachypneic (RR-28/min) with saturation being 68%. He had clubbing of fingers while the rest of the general physical examination was normal. During auscultation, he had bilateral coarse crepitation. Blood workup showed Leukocytosis (23160 cu mm), neutrophilic predominant, however, HsCRP, ACE levels were normal. ANA and RA factor was negative Arterial blood gases showed significant hypoxemia (PaO2 – 61.8mmHg). We repeated the chest X-ray (Figure 1) showing reticulonodular infiltrates, predominantly in the

upper zone, with sparing of the costo-phrenic angle. 2D- Echo was normal. Computerized tomography showed multiple cystic changes with intervening septal thickening, predominantly in the upper lobes, with streaky scarring and atelectasis. Basal sparing was seen (Figure 2 and 3). There were no abnormalities in the skin and skeleton of the patient with no pituitary dysfunction or any other related manifestation. The diagnosis of isolated Pulmonary Langerhans' cell histiocytosis was based on radiological findings. Bronchoscopy could not be performed owing to financial reasons and worsening hypoxemia. The patient received 3 days of pulse dose of methylprednisolone. He showed mild improvement in hypoxemia and was later was lost to follow up.

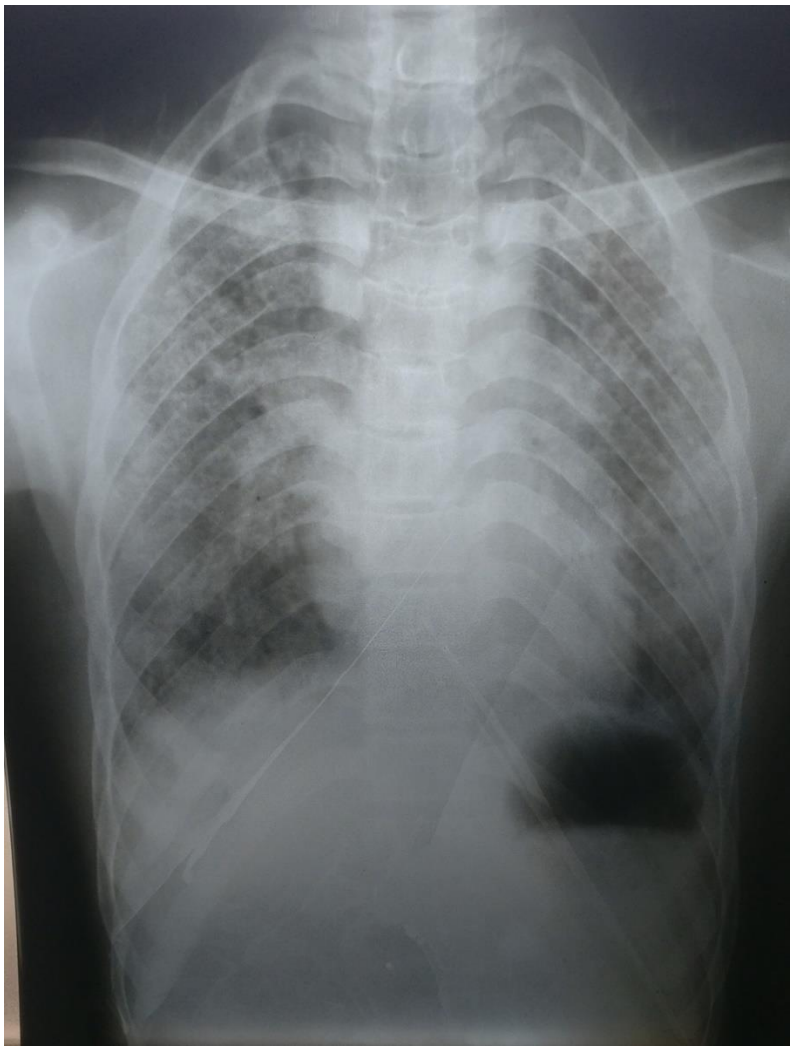

Figure 1: Chest X ray shows nodular opacities with upper zone predominance and costophrenic angle sparing.

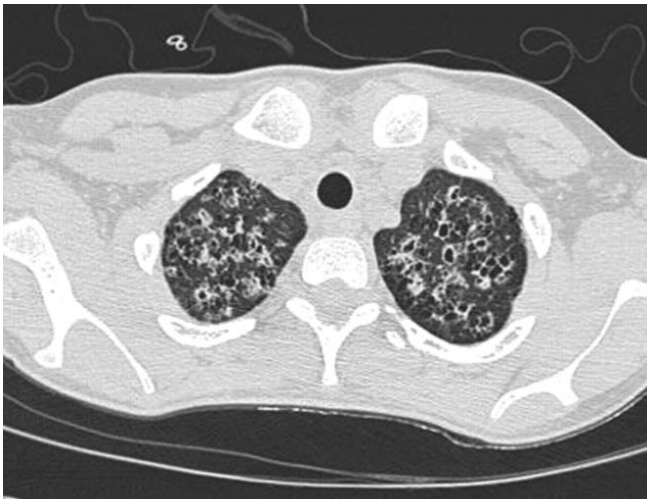

Figure 2: Diffuse lung cysts with parenchymal distortion.

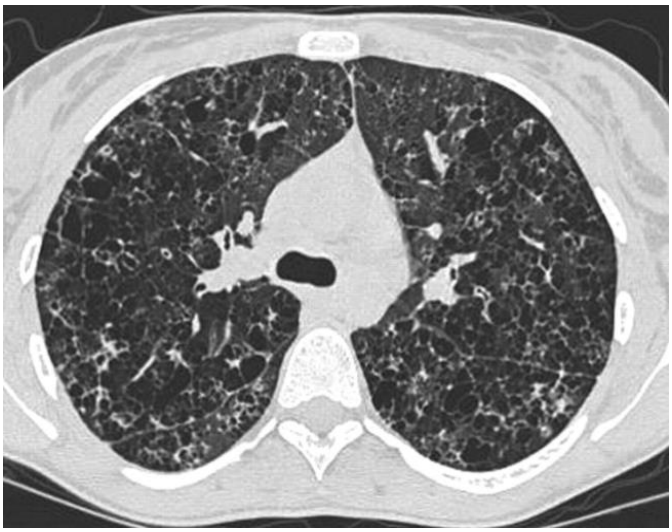

Figure 3: Intervening septal thickening seen, larger cysts, upper lobe predominance.

Discussion

The majority of adults (20-40 years of age) cases of LCH are limited to lung involvement and particularly associated with smoking. **(**4**)** Our case stands an exception to the age (being 16 years) and the patient being nonsmoker. Isolated pulmonary LCH is vanishingly rare in adolescents. **(**5**)** In an early series of >500 patients with diffuse infiltrating lung disease, surgical lung biopsy showed LCH in <5% of the cases **(**6**)**. As opposed to adults, pulmonary involvement in children mostly occurs as a form of multisystemic form of LCH, where it is present in 23% to 50% of cases; lung involvement is rarely the most predominant clinical presentation **(**7**)**.

The localized form of LCH has been previously referred to as Eosinophilic Granuloma, whereas the multisystem variant used to be known by a variety of names, including systemic histiocytosis X, Letterer – Siwe disease, and Hand-schullen-christian disease. To avoid this confusion, the histiocyte society has established a simplified classification system1(Table 1).

Table 1

SIMPLIFIED SYSTEM OF CLASSIFICATION OF LANGERHANS' CELL HISTIOCYTOSIS IN ADULTS
SINGLE ORGAN INVOLVEMENT 1. Lung (Occur in isolation in >85% cases with lung involvement) 2. Bone 3. Skin 4. Pituitary 5. Lymph nodes 6. Other sites: Thyroid, liver, Spleen, Brain **MULTI ORGAN INVOLVEMENT** 1. Multi organ with lung involvement (in 5-15% of cases in lung involvement) 2. Multi organ without lung involvement 3. Multi organ histiocytic disorder The terms formerly used for eosinophilic granuloma (for LCH with single organ involvement), Letterer-Siwe disease (for aggressive systemic form), Hand-schullen-christian disease (for triad of Exopthalmous, Diabetes insipidus, bone lesions, rarely seen in adults).

Isolated Pulmonary involvement in children is very rare mainly because of 2 reasons; first, it is mainly associated with cigarette smoking, which is less expected in children, unless passive smoking is ruled out. Second, although the isolated form may begin in childhood, and goes undetected until adulthood **(**8,9**)**.

Clinical presentation of the symptomatic lung in LCH in children is nonspecific, like dyspnea, cough, chest pain, wheeze, fatigue and tachypnea **(**10**)**. Sometimes, when the cysts are located subpleural, can rupture and cause pneumothorax.

Radiology plays a key role in diagnosing Pulmonary LCH. In our case, reticulonodular opacities with basal sparing on chest X-ray was our first clue. The characteristic finding on high-resolution computerized tomography (CT) include reticulonodular infiltrates in early disease and cystic changes in more advanced cases. The findings are symmetrical, predominant in the upper and middle lobes, with a costophrenic angle sparing **(**11,12,13**)**.

To obtain a definitive diagnosis, immunohistochemical demonstration of CD1a epitopes on the cell surface and/or demonstration on Birbeck granules on electron microscopy is required in addition to conventional light microscopy (and positive staining for S100 protein). Once LCH is diagnosed based on typical histological findings, it needs to be classified as a single system or multisystem disease (refer table 1) based on the number of organs involved **(**14**)**.

Though not a part of any diagnostic criteria, pulmonary function testing may help assess the baseline degree of impairment and to monitor response to treatment over time. This may be difficult to attain, owing to pediatric population. In one of the studies, it was noted that diffusion impairment occurred much earlier to the radiological changes **(**15**)**.

A multidisciplinary approach is taken in the treatment of the above disease. In adults, unlike children is most commonly associated with smoking, hence smoking cessation can result in significant clinical improvement associated with the resolution of the disease **(**3,16,17**)**.In adolescents, both firsthand and secondhand smoking/ vaping needs to be identified, and the patient is adequately counseled on cessation of the same.

A combination of glucocorticoids and vinblastine has been accepted as the first line of treatment as per international guidelines **(**16**)**. It has been studied to improve 5-year survival probability and reduce disease reactivation **(**18**)**. Other agents that can be used are Cytarabine (pyrimidine

analogue, inhibits DNA synthesis), Cladribine (purine analogue), Targeted Mitogen-activated tyrosine kinases (MAPK) therapy like Vemurafenib, Dabrafenib, or Trametinib. For patients with recurrent pneumothoraces, pleural intercoastal drainages will be helpful. Lung transplantation can be considered in end-stage lung disease or severe pulmonary hypertension.

It has been suggested that an altered immune response to tobacco glycoprotein, is a potential stimulator of macrophages including the production of IL-1, IL6 cytokines **(**19**)**. Another hypothesis is that the development of hyperplastic or dysplastic bronchiolar lesions may be involved in both accumulation and activation of Langerhans' cells in bronchioles **(**20**)**. With early diagnosis and appropriate treatment, the prognosis appears to be good with improvement in the diffusion impairment and radiological resolution **(**21,22**)**.

Conclusion

Isolated pulmonary LCH is extremely rare in adolescent children, often mistaken for military tuberculosis (in high burden countries like India) and CF/non CF bronchiectasis (in countries like the USA). The characteristic radiological findings with a smoking history should arise suspicion, and multisystem involvement should be looked for in children. Diagnosis to be made on immunohistochemistry studies. Chemotherapy and specific management of complications remain the mainstay treatment.

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